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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,075	09/09/2002	David G. Atkins	ATKINS1	6813

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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,075	ATKINS ET AL.	
	Examiner	Art Unit	
	J. D. Schultz, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-62* is/are pending in the application.

4a) Of the above claim(s) *59-62* is/are withdrawn from consideration.

5)☒ Claim(s) *20,22,23,26,28,29,32,34,35,38,40,41,44,46 and 48* is/are allowed.

6)☒ Claim(s) *21,24,25,27,30,31,33,36,37,39,42,43,45,47 and 49-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/10/01; 2/7/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Claim 1 is allowable. The restriction requirement among the inventions, as set forth in the Office action mailed on 5 April 2006, has been reconsidered in view of the allowability of claims to the elected invention pursuant to MPEP § 821.04(a). **The restriction requirement is hereby withdrawn as to Groups I-XV**. The restriction of Groups I-XV from that of Group XVI is maintained, since the generic claim embracing Groups I-XV does not embrace the invention of Group XVI.

In view of the above noted withdrawal of the restriction requirement, applicant is advised that if any claim(s) presented in a continuation or divisional application include all the limitations of a claim that is allowable in the present application, such claims may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Once a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

The requirement is still deemed proper and is therefore made FINAL.

Claims 59-62 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 17 January 2006.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. The disclosure contains sequences which fall under the purview of 37 CFR 1.821 through 1.825 as requiring SEQ ID NOS:, but which are not so identified. For example, the drawings contain multiple sequences in excess of 10 nucleotides long that are not identified by a SEQ ID NO:. Applicants should be aware that these sequences may not be the only instance necessitating this notice. Applicants should carefully review the application for any further examples of failures to identify any sequences by SEQ ID NO:, and to otherwise verify that the application is in compliance. In order to be considered fully responsive, Applicants response to the instant action must put the application into full sequence compliance, as this requirement will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21, 24, 25, 27, 30, 31, 33, 36, 37, 39, 42, 43, 45, and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21, 24, 25, 27, 30, 31, 33, 36, 37, 39, 42, 43, 45, and 47 all recite the limitation "the 3'-end nucleotide residue is inverted in the binding domain contiguous with the 3'-end of the catalytic domain." However, a 3'-end will only be continuous with a 5'-end of any nucleotide strand to which it is conjugated. Accordingly, the claim is considered indefinite, and clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for DNAzyme-mediated inhibition of EGR-1 expression *in vitro*, does not reasonably provide enablement for DNAzyme-mediated inhibition of EGR-1 expression *in vivo*, or for methods of treating diseases associated with its expression *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The above invention is drawn to methods of inhibiting the expression of EGR-1 in cells comprising contacting said cells or tissues with DNAzyme compositions that inhibit the expression of EGR-1, wherein the language of said claims encompasses both *in vivo* and *in vitro* activity. The claims of the above invention are also drawn to methods of treating an animal having a condition associated with EGR-1, wherein said compositions are administered to animals such that expression of EGR-1 is inhibited, wherein administration is to vascular or neoplastic cells, or wherein said conditions are associated with cell proliferation or migration

selected from the group consisting of post-angioplasty restenosis, vein graft failure, hypertension, transplant coronary disease, and complications associated with atherosclerosis or peripheral vascular disease.

The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims is drawn to methods broadly embracing methods of inhibiting EGR-1 or treatments comprising such inhibition. Notably, the nature of the invention is centered upon the inhibition of expression of a specific mRNA using nucleic acid therapeutics in the whole animal (i.e. *in vivo*). While the level of one of ordinary skill practicing the instant invention would be high, the level of predictability is considered to be extremely variable as evident in the prior art (discussed in detail below), and is not considered to provide, in and of itself, sufficient enablement to practice the invention as claimed. Moreover, the amount of direction provided by the inventor (also discussed below) is similarly lacking, since the disclosed guidance depends explicitly, and almost entirely, on the teachings of the prior art. The working examples are not considered to support the breadth of the invention as instantly claimed, also for reasons provided below. The quantity of experimentation needed to make or use the invention based on the content of the disclosure alone is therefore not enabling for practice of the instant invention *in vivo*.

The specification teaches prophetic methods of treatment using DNAzyme oligos targeted to EGR-1, with broad treatment regimens that include pharmaceutical formulations, and treatment regimens. The specification exemplifies only methods of using the claimed compositions to inhibit the expression of EGR-1 in cultured cells *in vitro*, and in methods of directly applying the DNAzyme to the desired site surgically or through a stent. Such prophetic methods and exemplification are not considered sufficient to overcome the *in vivo* delivery concerns evident throughout the art as cited below.

Turning to the state of the art prior art, a thorough review of the field clearly indicates that inhibition of gene expression utilizing oligonucleotide therapeutics *in vitro* is routine. Although the use of DNAzymes is relatively undescribed, the field is well described in regards to the in vitro use of a similar technology, that of antisense oligonucleotides. Accordingly, since the issues that give rise to unpredictability that apply to antisense oligonucleotides also apply to the use of DNAzyme oligonucleotides, the art of antisense is summarized herein.

It is maintained that *in vivo* inhibition of gene expression at the time of filing and even to the present time is not routine for several reasons, primarily due to the problem of delivery, and to a lesser extent, specificity and length of bioactivity. The problem of delivery results from the poor ability of nucleic acid therapeutic to reach the appropriate target cell, and penetrate the membrane (or membranes, since they are typically taken into lysosomes) in sufficient concentrations such that the target gene is inhibited to a degree necessary to result in a therapeutic effect.

The following references are cited herein to illustrate the state of the art in support of the statements.

For example, Jen et al. (Stem Cells 2000, Vol. 18, p 307-319) indicates "[o]ne of the major limitations for the therapeutic use of AS-ODNs and ribozymes is the problem of delivery.... presently, some success has been achieved in tissue culture, but efficient delivery for in vivo animal studies remains questionable...Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the DNAzyme strategy has proven elusive.

Opalinska et al. (Nature Reviews Drug Discovery, 2002, vol 1, p. 503-514) states "it is widely appreciated that the ability of nucleic-acid molecules to modify gene expression in vivo is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA". From column 2 of the same page, "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

A review article by Braasch et al. concludes that major obstacles persist in the art of using nucleic acid therapeutics in treating disease: "gene inhibition by amtisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially

unreliable" (Pg. 4503, para. 1 and 2). Braasch et al. specifically identify 3 factors that contribute to the unpredictable efficacy of using oligomeric compounds in general: 1) the variable capability of oligonucleotides to access sites within the mRNA to be targeted; 2) problems pertaining to the delivery and uptake of the oligomers by cells, with the result that "the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death"; and 3), that "oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism.

Regarding the difficulties of predicting whether oligonucleotides can access sites within their target mRNA, Braasch et al. elaborates, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column).

Branch et al. discuss the problems pertaining to non-specific oligo interactions that lead to artifactual phenotypes during *in vivo* oligomeric administration: "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis" (Page 50), while Tamm et al. states that "[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 493, right column).

Further, regarding the therapeutic benefit of oligomeric technology in general, Branch states that "in fact, nucleic acid drugs should not be thought of as magic bullets. Their therapeutic use will require vigilant monitoring. Compared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs extend only across a narrow concentration range. Both *in vitro* and *in vivo*, less than a factor of ten often separates the concentration producing no antisense effect form that producing the full antisense effect. Steep dose-response curves commonly indicate that a drug has multiple, synergistic mechanisms of action. A drug with a narrow therapeutic window can be potent and extremely valuable, but can also be tricky to use safely. Since the ratio of antisense to non-antisense effects drops sharply outside a restricted concentration range, it will be challenging to obtain consistent therapeutic benefit (Page 46, second column).

Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

Finally, Branch states that "[i]t is not yet clear whether *in vitro* screening techniques of the sort used by Milner and co-workers will identify ODNs that are effective *in vivo*. With so many possible sequences to choose from, and the likelihood that *in vitro* studies will not always predict *in vivo* efficacy, straightforward new screening techniques need to be developed for use in cells."

Thus, it is maintained that the specification, which depends largely upon the state of the prior art for enablement across the claimed scope, would not enable claims directed to the *in vivo*

use of oligomers, let alone claims directed to therapeutic use *in vivo*, because, a person skilled in the art would recognize that predicting the efficacy of an oligomeric compound *in vivo* based solely on its performance *in vitro* is unpredictable. Accordingly, one skilled in the art, being unable to use the prior art for such guidance, must necessarily find such guidance from the specification.

The specification as filed does not provide sufficient guidance or appropriate examples that would enable a skilled artisan to use the disclosed compounds or methods of using said compounds in *in vivo* environments, because the specification teaches only prophetic methods of treatment using DNAzyme oligos, or methods comprising direct delivery to the area of injury. The specification does not teach any specific treatment regimen that is specific for any DNAzyme oligonucleotide, but rather relies upon the guidance of the prior art in enabling one of skill to practice the instantly claimed treatment methods.

In order to practice the claimed invention *in vivo* in an organism a number of variables would have to be optimized, including 1) the form of the DNAzyme oligonucleotide, whether to use a modified oligonucleotide with one or more backbone, sugar or base modifications, 2) the mode of delivery of the DNAzyme oligonucleotide to an organism that would allow it to reach the targeted cell, 3) the amount of DNAzyme oligonucleotide that would need to be delivered in order to bind a sufficient amount of EGR-1 to reduce protein expression once it reached the proper cell and 4) ensuring the DNAzyme oligonucleotide remains viable in a cell for a period of time that allows inhibition of EGR-1 to an extent that there is a measurable and significant therapeutic effect. Each one of these variables would have to be empirically determined for each DNAzyme oligonucleotide. While optimization of any single one of these steps may be routine,

when taken together the amount of experimentation required becomes such that one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation.

Allowable Subject Matter

Claims 20, 22, 23, 26, 28, 29, 32, 34, 35, 38, 40, 41, 44, 46, 48 are allowed, since the prior art does not teach or suggest making or using DNAzymes targeted to nucleotides 168-332 of EGR-1 of SEQ ID NO: 1.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. D. Schultz, Ph.D. whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JDS

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER